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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,113	02/28/2006	Mariagrazia Pizza	PAT051720-US-PCT	8533

27476 7590 02/14/2011

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EXAMINER	
TONGUE, LAKIA J	

ART UNIT	PAPER NUMBER
1645	

MAIL DATE	DELIVERY MODE
02/14/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,113	PIZZA ET AL.	
	Examiner	Art Unit	
	LAKIA J. TONGUE	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 11-19* is/are pending in the application.

4a) Of the above claim(s) *13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,11,12 and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/2/10 and 12/6/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 6, 2010 has been entered. Claims 1-8 and 11-19 are pending. Claims 13-18 were previously withdrawn. Claims 1-8, 11, 12 and 19 are currently under examination.

Information Disclosure Statement

2. The information disclosure statement (IDS) submitted on August 2, 2010 and December 6, 2010 is in compliance with the provisions of 37 CFR 1.97 and has been considered. An initialed copy is attached hereto.

Rejections Withdrawn

3. In view of Applicant's arguments, the rejection of claims 1-3, 5-7, 11 and 12 under 35 U.S.C. 102(e) as being anticipated by Gorringe et al. (WO 01/73080 A2) is withdrawn.

4. In view of Applicants arguments, the rejection of claims 1-8, 11,12 and 19 under 35 U.S.C. 103(a) as being unpatentable over Morein et al. (Analytical Biochemistry, 1994; 216: 47-51) in view of Gorringe et al. (WO 01/73080 A2) as applied to claims 1-3,

5-7, 11 and 12 above, and van der Ley et al. (Vaccine; 1995; 13(4): 401-407) and further in view of Rosenqvist et al. (WO 01/91788 A1) is withdrawn.

New Grounds of Objection and Rejection

Claim Objections

5. Claims 1 and 19 are objected to because of the following informalities: In claim 1, on first site "*N. meningitidis* and *N. gonorrhoeae*" should be written "*Neisseria meningitidis* or *Neisseria gonorrhoeae*. Claim 19 has misspelled meningitidis. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 4 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is rendered vague and indefinite by the use of the terms "sterile filtration". It is unclear what is intended by said terms, as it is not explicitly defined in the specification. The term sterile refers to something that is free from microorganisms. The term "sterile filtration" could therefore mean filtration of a liquid that is free from microorganisms. Based on the use of the terms in the specification, it appears that applicant intends the terms to refer to filtration of a non-sterile substance in order to

make it sterile; however, this is not clear based on the terms itself. Additionally, the terms are further unclear because the specification indicates the use of ultrafiltration, which would not necessarily remove viruses. As written, it is impossible to determine the metes and bounds of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

7. Claims 1-3, 5-7, 11, 12 and 19 are rejected under 35 U.S.C. 102(e) as being anticipated by Granoff et al. (U.S. Patent 6,936,261 B2; Filed: 7/27/01).

Independent claim 1 is drawn to a process for the manufacture of an outer membrane vesicle preparation from a bacterium, wherein the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the outer membrane vesicle preparation and the bacterium is *N. meningitidis* or *N. gonorrhoeae* and over expresses TbpA, Transferrin binding protein A, relative to the corresponding wild-type strain.

Granoff et al. disclose a method of preparing outer membrane vesicles. The cell suspension was then sonicated on ice with several 15-second bursts using a

microprobe sonifier (Branson, Danbury, Conn.). Cell debris was removed by centrifugation at 16,000xg for 15 min., and the outer membrane vesicles (OMVs) in the supernatant were obtained by ultracentrifugation at 100,000xg for 2 hrs. at 4°C. The OMV pellet was resuspended in 2 ml of water ("OMV" vaccine preparation). Alternatively, the frozen cell pellet was resuspended in 0.1M Tris. HCl. After stirring for 30 min. at ambient temperature, the mixture was centrifuged (20,000xg, 30 min., 4°C). The supernatant was retained and the pellet was reextracted and centrifuged again with one third volume of the same buffer (see column 32, lines 39-52). Granoff et al. disclose that the OMV preparations were diluted in PBS and either mixed with an equal volume of complete Freund's adjuvant (CFA; Sigma Chemical Company, St. Louis, Mo.) or aluminum hydroxide (see column 32, lines 62-65). Granoff et al. disclose the use of an outer membrane vesicle vaccine prepared from a single *Neisseria meningitidis* serogroup B strain, H44/76 (B:15:P1.7,16; "Norwegian vaccine") (see column 4, lines 7 and 10-14).

The method steps and bacterium (*Neisseria meningitidis* serogroup B strain H44/76) of Granoff et al. are identical to the method steps and bacterium recited in the claimed invention as well as those used in the instant specification. The outer membrane vesicle preparation from said bacterium, absent evidence to the contrary, necessarily over expresses TbpA, relative to a corresponding wild-type strain.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Please note, in light of the 112/2 set forth above, it is not clear what is intended by the terms "sterile filtration." As it appears, from the specification, the term refers to filtration of a non-sterile substance to create a sterile substance; consequently, this is the way it is being interpreted for the purposes of this rejection.

8. Claims 1-8, 11, 12 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Granoff et al. (U.S. Patent 6,936,261 B2; Filed: 7/27/01), and further in view of Reeves et al. (Gene Therapy, 2000; 7: 1993-1998).

Independent claim 1 is drawn to a process for the manufacture of an outer membrane vesicle preparation from a bacterium, wherein the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the outer membrane vesicle preparation and the bacterium is *N. meningitidis* or *N. gonorrhoeae* and over expresses TbpA, Transferrin binding protein A, relative to the corresponding wild-type strain.

Dependent claim 4 is drawn to a process for the manufacture of an outer membrane vesicle preparation from a bacterium, wherein the bacterial membrane is disrupted substantially in the absence of deoxycholate detergent to produce the outer

membrane vesicle preparation and the bacterium is *N. meningitidis* or *N. gonorrhoeae* and over expresses TbpA, Transferrin binding protein A, relative to the corresponding wild-type strain comprising the following basic steps: (a) disrupting the bacterial membrane in the substantial absence of detergent; (b) centrifuging the composition from step (a) to separate the outer membrane vesicles from treated cells and cell debris, and collecting the supernatant; (c) performing a high speed centrifugation of the supernatant from step (b) and collecting the outer membrane vesicles in a pellet; (d) re-dispersing the pellet from step (c) in a buffer; (e) performing a second high speed centrifugation in accordance with step (c), collecting the outer membrane vesicles in a pellet; (f) re-dispersing the pellet from step (e) in an aqueous medium; further comprising: (g) performing sterile filtration through at least two filters of decreasing pore size of the re-dispersed composition from step (f); and (h) optionally including the composition from step (g) in a pharmaceutically acceptable carrier and/or adjuvant composition.

Dependent claim 8 is drawn to the process of claim 4, wherein the step (g) ends with a filter of pore size of about 0.2 µm.

Granoff et al. disclose a method of preparing outer membrane vesicles. The cell suspension was then sonicated on ice with several 15-second bursts using a microprobe sonifier (Branson, Danbury, Conn.). Cell debris was removed by centrifugation at 16,000xg for 15 min., and the outer membrane vesicles (OMVs) in the supernatant were obtained by ultracentrifugation at 100,000xg for 2 hrs. at 4°C. The OMV pellet was resuspended in 2 ml of water ("OMV" vaccine preparation).

Alternatively, the frozen cell pellet was resuspended in 0.1M Tris. HCl. After stirring for 30 min. at ambient temperature, the mixture was centrifuged (20,000xg, 30 min., 4°C). The supernatant was retained and the pellet was reextracted and centrifuged again with one third volume of the same buffer (see column 32, lines 39-52). Granoff et al. disclose that the OMV preparations were diluted in PBS and either mixed with an equal volume of complete Freund's adjuvant (CFA; Sigma Chemical Company, St. Louis, Mo.) or aluminum hydroxide (see column 32, lines 62-65). Granoff et al. disclose the use of an outer membrane vesicle vaccine prepared from a single *Neisseria meningitidis* serogroup B strain, H44/76 (B:15:P1.7,16; "Norwegian vaccine") (see column 4, lines 7 and 10-14).

The method steps and bacterium (*Neisseria meningitidis* serogroup B strain H44/76) of Granoff et al. are identical to the method steps and bacterium recited in the claimed invention as well as those used in the instant specification. The outer membrane vesicle preparation from said bacterium, absent evidence to the contrary, necessarily over expresses TbpA, relative to a corresponding wild-type strain.

Granoff et al. do not specially disclose (g) performing sterile filtration through at least two filters of decreasing pore size of the re-dispersed composition from step (f); and (h) optionally including the composition from step (g) in a pharmaceutically acceptable carrier and/or adjuvant composition, as recited in claim 4 or that step (g) ends with a filter of pore size of about 0.2 µm, as recited in claim 8.

Reeves et al. disclose methodologies which increase production volume while maximizing titer of a manufactured product. Reeves et al. disclose that to obtain cell-

free material, one utilizes filter systems ranging from 0.2 to 0.45 micron pore size which are commercially available and well suited for use in processing small to moderate volumes of supernatant (less than a liter). Reeves et al. disclose that a series of filters with decreasing pore sizes may provide more rapid filtration than single pore size filters and would also improve recovery of particles yielding higher titer of the manufactured material. Moreover, Reeves et al. disclose a step filtration system for processing large volumes of supernatant. The components of this system are filtration devices currently approved for clinical use. The components can be joined using a sterile connecting device to form a closed system decreasing the risk of contamination (page 1993; Introduction).

Limitations such as the end size of a pore size filter are being viewed as limitations of optimizing experimental parameters.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Granoff et al. with the teachings of Reeves et al. to perform sterile filtration through at least two filters of decreasing pore size of the re-dispersed composition from step (f) because filtering the re-dispersed composition from step (f) through a series of filters of decreasing pore size can decrease filtration time by removing large debris before it can obstruct filtration through small pore filters. Unobstructed filtration should generate less shear forces, allowing higher flow rates, quicker freezing and result in higher titer of the final product (see Reeves; page 1993; Results and discussion).

One would have had a reasonable expectation, barring evidence to the contrary, that the method would be effective for a process for preparing bacterial outer membrane vesicle from a bacterium.

Since the claimed method steps were known in the prior art and one skilled in the art could have combined the steps as claimed by known methods with no change in their respective functions and the combination would have yielded predictable results to one of ordinary skill in the art at the time of the invention. See the recent Board decision *Ex parte Smith,--USPQ2d--,* slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing *KSR, 82 USPQ2d* at 1396).

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAKIA J. TONGUE whose telephone number is (571)272-2921. The examiner can normally be reached on Monday-Friday 8-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Patricia Duffy can be reached on 571-272-0855. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LJT
1/28/11

/Vanessa L. Ford/

Primary Examiner, Art Unit 1645